Claims

1. An antibody against a human CD40 or a functional fragment thereof, having at least one property selected from the following properties (a) to (f) of:

   (a) acting on dendritic cells to produce IL-12 in the presence of LPS and IFNγ;
   (b) having activity to act on dendritic cells causing the cells to mature, which is higher than that of a G28-5 antibody;
   (c) having activity to promote an established B cell line to express CD95, which is higher than that of the G28-5 antibody;
   (d) having activity to suppress the proliferation of an established B cell line, which is higher than that of the G28-5 antibody;
   (e) inducing cell death of an established B cell line; and
   (f) not inhibiting the binding of CD40 ligands to CD40.

2. The antibody or the functional fragment thereof of claim 1, wherein the maturation of dendritic cells is performed at an antibody concentration of 20 μg/ml or less.

3. The antibody or the functional fragment thereof of claim 1, promoting the established B cell line to express CD95 at an antibody concentration of 20 μg/ml or less.

4. The antibody or the functional fragment thereof of claim 1, wherein the established B cell line is Ramos or HS-Sulton.

5. The antibody or the functional fragment thereof of claim 1, wherein the production of 100 pg/ml or more IL-12 is provided when the antibodies with a concentration of 0.1 μg/ml or more are added to dendritic cells with a concentration of 1×10^6 cells/ml.

6. The antibody or the functional fragment thereof of claim 1, wherein the production of 1000 pg/ml or more IL-12 is provided when the antibodies with a concentration of 1 μg/ml or more are added to dendritic cells with a concentration of 1×10^6 cells/ml.

7. The antibody or the functional fragment thereof of claim 1, wherein the production of 10000 pg/ml or more IL-12 is provided when the antibodies with a concentration of 1 μg/ml or more are added to dendritic cells with a concentration of 1×10^6 cells/ml.

8. The antibody or the functional fragment thereof of claim 1, promoting within the antibody concentration range between 0.01 μg/ml and 10 μg/ml the established B cell line (Ramos cell) to express CD95 with approximately 2 to 3 times or more greater effectiveness than that expressed by a G28-5 antibody as a control.

9. The antibody or the functional fragment thereof of claim 1, promoting with an antibody concentration of 0.01 μg/ml the established B cell line (Ramos cell) to express CD95 with approximately 2 to 6 times or more greater effectiveness than that expressed by a G28-5 antibody as a control.

10. The antibody or the functional fragment thereof of claim 1, promoting with an antibody concentration of 0.1 μg/ml the established B cell line (Ramos cell) to express CD95 with approximately 2 to 7 times or more greater effectiveness than that expressed by a G28-5 antibody as a control.

11. The antibody or the functional fragment thereof of claim 1, promoting with an antibody concentration of 1 μg/ml the established B cell line (Ramos cell) to express CD95 with approximately 2 to 7 times or more greater effectiveness than that expressed by a G28-5 antibody as a control.

12. The antibody or the functional fragment thereof of claim 1, promoting with an antibody concentration of 10 μg/ml the established B cell line (Ramos cell) to express CD95 with approximately 2 to 6 times or more greater effectiveness than that expressed by a G28-5 antibody as a control.

13. An antibody or a functional fragment thereof, having the amino acid sequences of a heavy chain variable region and a light chain variable region of an antibody that is produced by a hybridoma KM302-1 (Accession No: FERM

BP-7578), KM341-1-19 (Accession No: FERM BP-7759), 2105 (Accession No: FERM BP-8024) or F1-102 (Accession No: ATCC PTA-3337).

14. An antibody or a functional fragment thereof, having amino acid sequences of the mature portions of a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma F2-103, which are respectively encoded by plasmid DNAs with Accession Nos. ATCC PTA-3302 and ATCC PTA-3303; a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma F5-77, which are respectively encoded by plasmid DNAs with Accession Nos. ATCC PTA-3304 and ATCC PTA-3305; or a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma F5-157, which are respectively encoded by plasmid DNAs with Accession Nos. ATCC PTA-3306 and ATCC PTA-3307.

15. An antibody or a functional fragment thereof, having amino acid sequences of the mature portions of a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma KM341-1-19, which are respectively represented by SEQ ID NOS: 28 and 30; a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma 2105, which are respectively represented by SEQ ID NOS: 32 and 34; a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma 110, which are respectively represented by SEQ ID NOS: 36 and 38; a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma 115, which are respectively represented by SEQ ID NOS: 40 and 42; a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma KM643-4-11, which are respectively represented by SEQ ID NOS: 52 and 54; a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma F2-103, which are respectively represented by SEQ ID NOS: 60 and 62; or a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma F5-77, which are respectively represented by SEQ ID NOS: 64 and 66.

16. An antibody or a functional fragment thereof, having amino acid sequences of the mature portions of a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma KM341-1-19, which are respectively represented by SEQ ID NOS: 27 and 29; a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma 2105, which are respectively represented by SEQ ID NOS: 31 and 33; a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma 110, which are respectively represented by SEQ ID NOS: 35 and 37; a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma 115, which are respectively represented by SEQ ID NOS: 39 and 41; a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma KM643-4-11, which are respectively represented by SEQ ID NOS: 51 and 53; a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma F2-103, which are respectively represented by SEQ ID NOS: 59 and 61; or a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma F5-77, which are respectively represented by SEQ ID NOS: 63 and 65.

17. An antibody against a human CD40, or a functional fragment thereof, having at least one property selected from the following properties (g) to (j) of:

(g) neutralizing the action of ligands for CD40;
(h) neutralizing or alleviating one or more effects that ligands, which are for CD40 on an established B cell line, have on CD40-expressing cells, and having agonistic action on CD40 on the established B cell line weaker than that of 5D12 due to cross-linking by anti-immunoglobulin antibodies;
(i) alleviating or neutralizing the action of CD40 ligands on the established B cell line to increase CD95 expression; and
(j) having antagonistic action on CD40 expressed on dendritic cells.

18. The antibody or the functional fragment of claim 17, which can suppress the expression of CD95 in Ramos cells to a level approximately 10% or less than that of a control, when antibodies with a concentration of 0.1 μg/ml are added to the Ramos cells with a concentration of 1×10^6 cells/in] supplemented with a saturated amount of CD40L-expressing cells.

19. The antibody or the functional fragment of claim 17, which can suppress the expression of CD95 in Ramos cells to the same level as that of a negative control, when the antibodies with a concentration of 1 μg/ml are added to the Ramos cells with a concentration of 1×10^6 cells/ml supplemented with a saturated amount of CD40L-express-

ing cells.

20. The antibody or the functional fragment of claim 17, which can suppress the expression of CD95 in the Ramos cells to the same level as that of the negative control, when the antibodies with a concentration of 10 μg/ml are added to the Ramos cells with a concentration of 1×10^6 cells/ml supplemented with a saturated amount of CD40L-expressing cells.

21. The antibody or the functional fragment of claim 17, wherein the proliferation of tonsillar B cells is suppressed in vitro by approximately 80 to 95% or more, when the antibodies with a concentration between 0.001 μg/ml and 10 μg/ml are added to 1×10^5 tonsillar B cells supplemented with soluble CD40L (1μg/ml).

22. The antibody or the functional fragment of claim 17, wherein the proliferation of tonsillar B cells is suppressed in vitro by approximately 95% or more, when the antibodies with a concentration between 0.01 μg/ml and 10 μg/ml are added to 1×10^5 tonsillar B cells supplemented with soluble CD40L (1μg/ml).

23. The antibody or the functional fragment of claim 17, wherein the proliferation of tonsillar B cells is suppressed in vitro by approximately 80% or more, when the antibodies with a concentration of 0.001 μg/ml are added to 1×10^5 tonsillar B cells supplemented with soluble CD40L (1μg/ml).

24. An antibody or a functional fragment thereof, having amino acid sequences of a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma KM281-1-10 (Accession No: FERM BP-7579), 4D11 (Accession No: FERM BP-7758) or F4-465 (Accession No: ATCC PTA-3338).

25. An antibody or a functional fragment thereof, having amino acid sequences of the mature portions of a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma KM281-1-10, which are respectively represented by SEQ ID NOS: 44 and 46; a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma 4D11, which are respectively represented by SEQ ID NOS: 48 and 50; or a heavy chain variable region and a light chain variable region of the antibody produced by a hybridoma F4-465, which are respectively represented by SEQ ID NOS: 56 and 58.

26. An antibody or a functional fragment thereof, having amino acid sequences of the mature portions of a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma KM281-1-10, which are respectively represented by SEQ ID NOS: 43 and 45; a heavy chain variable region and a light chain variable region of an antibody produced by a hybridoma 4D11, which are respectively represented by SEQ ID NOS: 47 and 49; or a heavy chain variable region and a light chain variable region that are encoded by nucleic acid sequences isolated from a hybridoma F4-465, which are respectively represented by SEQ ID NOS: 55 and 57.

27. The antibody or the functional fragment thereof of any one of claims 1 to 26, which is a human antibody.

28. A pharmaceutical composition, containing as an active ingredient the antibody or the functional fragment thereof of any one of claims 1 to 26.

29. An immunopotentiating agent, anti-tumor agent or anti-autoimmune disease agent, containing as an active ingredient the antibody or the functional fragment thereof of any one of claims 1 to 16.

30. An immunosuppressive agent, anti-autoimmune disease agent, therapeutic agent against allergies or therapeutic agent against blood coagulation factor VIII -inhibiting syndrome, containing as an active ingredient the antibody or the functional fragment thereof of any one of claims 17 to 26.